1 Environmental considerations for risk/safety assessment for the release of transgenic plants

This document deals with the environmental risk/safety assessment (biosafety) at a broad level. It provides general information on key concepts and points that risk/safety assessors should focus on when planning risk/safety assessments for the release of transgenic plants into the environment: comparative approach, familiarity with the biology of the unmodified plant species, general protection goals, assessment endpoints, potential adverse effects associated with the environmental release, pathways to harm and corresponding risk hypotheses, information elements, and the use of environmental considerations in planning such assessment. Annexes A to G describe seven examples of environmental considerations routinely examined and taken from actual experience gained during risk/safety assessment of transgenic plants intended for environmental release.

1.1. Purpose of the document

The purpose of this document is to illustrate how a set of environmental considerations can be used to inform the planning and structure of an environmental risk/safety assessment for release of a transgenic plant.

The environmental considerations included in the annexes to this document were drawn from the collective knowledge of risk/safety assessors with experience in evaluating the environmental risk/safety of transgenic plants. This set of considerations captures many of the types of interactions that can occur between a transgenic plant and its receiving environment that are widely considered under various national and regional legal frameworks. They include invasiveness and weediness, vertical gene flow, organisms (animals), soil functions, plant health, crop management practices, and biodiversity (protected species and habitats/ecosystems). This set is not meant to be prescriptive or exhaustive and these considerations may be treated differently among jurisdictions.

For each environmental consideration listed above, Annexes A-G give examples of how the approach described in the next section, Planning an Environmental Risk/Safety Assessment, can facilitate the development of plausible pathways to harm to an environmental value to be protected, the formulation of corresponding risk hypotheses, and the identification of information relevant to evaluate those hypotheses. Conducting the subsequent environmental risk/safety assessment is not covered in this document. The paradigm of risk assessment has been elaborated in an earlier OECD document (OECD, 1993).

Key concepts and terms are described, including for each environmental consideration, but in some cases, they may be defined slightly differently dependent on the context, including authorship, scientific field, or jurisdiction. Even within the environmental risk/safety assessment literature (e.g. OECD, 2003; IPCS, 2004; EFSA, 2012), depending on the type of assessment, legislation, jurisdictional, or institutional framework, etc., different terms may be used to describe similar concepts. However, the purpose of this document is not to elaborate on or establish new terminology but rather to describe a process and provide illustrative examples for planning an environmental risk/safety assessment.

This document builds on the work begun by the OECD that first articulated some of the key concepts that form the context and basis for conducting an environmental risk/safety assessment: *Recombinant DNA Safety Considerations* (the so-called “Blue Book”; OECD, 1986), *Safety Considerations for Biotechnology* (OECD, 1992), and *Safety Considerations for Biotechnology: Scale-up of Crop Plants* (OECD, 1993). These concepts, which have been adopted and articulated elsewhere (UNEP, 1995; SCBD, 2000; IPPC, 2019), include: the step-by-step approach to environmental release; the case-by-case and comparative nature of the assessment; the importance of familiarity; and consideration of the characteristics of the organism, the introduced trait, the receiving environment, and the interactions among them.

Companion documents prepared by the OECD Working Party on the Harmonisation of Regulatory Oversight in Biotechnology provide additional support for the environmental risk/safety assessment of transgenic plants. These include:

- Consensus Document on Molecular Characterisation of Plants Derived from Modern Biotechnology (OECD, 2010)
- Revised Points to Consider for Consensus Documents on the Biology of Cultivated Plants (OECD, 2020)
- Series of biology of plants consensus documents (OECD, 1997 to 2021+)
- Series of trait consensus documents (OECD, 1996 to 2007+)

Taken together, this comprehensive package of OECD documents is intended to inform those conducting environmental risk/safety assessments of transgenic plants, support OECD collaborations and

discussions, provide key documents both for countries that have established regulatory systems and for those establishing regulatory systems and capabilities, and inform other interested stakeholders.

1.2. Planning an environmental risk/safety assessment

Key concepts used throughout the environmental risk/safety assessment of a transgenic plant include the comparative nature of the assessment, and familiarity with the characteristics of the plant species, the introduced trait, the receiving environment, and the interactions among them. Furthermore, the assessor abides by the relevant national or regional legislation.

1.2.1. Comparative approach

Environmental risk/safety assessments typically use a comparative approach. The differences between a particular transgenic plant and a comparator provide a starting point for determining if the release of the transgenic plant might result in potential adverse effects on the environment. The transgenic plant is typically compared to a non-modified plant with a genotype that is as closely related as possible to the transgenic plant. However, there is no single concept of an appropriate comparator that is agreed upon internationally. In some instances, where the regulatory framework permits, the comparator may be another transgenic plant. Furthermore, more than one comparator may be used in a risk/safety assessment (though for simplicity, in this document, the singular 'comparator' is used). The choice of comparator can depend on the scientific questions to be considered and other factors, such as the availability of appropriate comparators and specific regulatory requirements.

When a relevant difference is identified between the transgenic plant and a comparator, it is evaluated to determine if it is significant and has biological relevance related to a jurisdiction's protection goals (see below). The variation within cultivated varieties of the plant species is usually considered to put any identified differences between the transgenic plant and the comparator into context.

1.2.2. Familiarity

Familiarity arises from knowledge of and experience with the biology of the unmodified plant, the introduced trait, and the receiving environment (OECD 1993), and plays a key role in setting the context for the environmental risk/safety assessment.

Familiarity with the plant might derive from, but is not limited to, knowledge of the plant's taxonomy and genetics, morphological characteristics, and reproductive biology. For additional information, see Revised Points to Consider for Consensus Documents on the Biology of Cultivated Plants (OECD, 2020).

Familiarity with the introduced trait might derive from, but is not limited to, knowledge of the function of the DNA sequence in its source organism, the function of the DNA sequence in the transgenic plant, and the resulting phenotype of the transgenic plant.

Familiarity with the receiving environment might derive from, but is not limited to, knowledge of the habitats available to the transgenic plant, presence and habitats of sexually-compatible species including wild relatives, centre(s) of origin and distribution, presence of species of conservation concern, provision of ecological functions, climate, growing season, presence of abiotic and biotic stressors, and types of crop management practices used, among others. The receiving environment can differ between and within regions. Therefore, consideration is given to the region where the transgenic plant will be cultivated or could reasonably be expected to grow.

The receiving environment to be considered could include both managed and unmanaged ecosystems, depending on a jurisdiction's legislative framework. There are no internationally-agreed definitions for managed and unmanaged ecosystems so for the purpose of this document, managed ecosystems

are considered to include production areas for agriculture (including field margins), horticulture, and forestry, and intensive land use areas such as roadsides and urban areas. Unmanaged ecosystems include natural areas, protected reserves and parks, and other areas with minimal human intervention.

During the initial steps of the environmental risk/safety assessment of a transgenic plant intended for release, the assessor plans how to proceed with the assessment. The initial steps of the assessment can build from what is often referred to as problem formulation in the environmental risk assessment literature (Suter, 2007; Wolt et al., 2010) and include the following steps:

- Identifying general (and, when needed, operational) protection goals.
- Determining assessment endpoints.
- Identifying potential adverse effects on the assessment endpoints associated with the release of the transgenic plant.
- Identifying plausible pathways to harm to the assessment endpoints and formulating corresponding risk hypotheses for each step of the pathway.
- Determining information elements relevant to evaluating the risk hypotheses.

Subsequent steps in the risk/safety assessment, for example collecting appropriate information and data to establish the validity of the risk hypotheses identified in the planning stage, risk characterisation and decision making, fall outside the scope of this document.

1.2.3. General protection goals

General protection goals establish the context for the environmental risk/safety assessment. They describe components of the environment (e.g. species, habitats, services, etc.) that are generally identified in the relevant existing laws or policies of a jurisdiction as valued and/or protected. Specific components of the environment may be valued for their aesthetic, cultural or intrinsic value, or because they are explicitly protected by law (e.g. organisms classified as threatened or endangered). General protection goals cover broad concepts and are similar between regulatory authorities, although they may be described using different terminology. An example of a general protection goal relevant to the environmental risk/safety assessment of a transgenic plant could be ‘sustainability of ecosystem services’.

1.2.4. Assessment endpoints

Assessment endpoints are derived from general protection goals and are explicit expressions of the environmental value to be protected. Assessment endpoints can be further defined as a valued ecological entity and an attribute that can be estimated by measurement or modelling. When general protection goals are too broad to translate directly into assessment endpoints, operational protection goals derived from the general protection goals may be used as an intermediate step to facilitate the determination of assessment endpoints (Garcia-Alonso and Raybould, 2014; Devos et al., 2015). For example, the general protection goal ‘sustainability of ecosystem services’ could be refined into several operational protection goals, notably ‘maintaining pollination services’, then further into assessment endpoints, each consisting of an entity and an attribute. The entity for ‘maintaining pollination services’ could be pollinators/honeybees, and its attributes could be at organism-level (e.g. pollinator/honeybee survival) and/or at population-level (e.g. pollinator/honeybee abundance) (U.S. EPA, 2007). It should be noted that in an environmental risk/safety assessment it is often necessary to consider a number of assessment endpoints to address each general or operational protection goal.

1.2.5. Potential adverse effects associated with the environmental release of a transgenic plant

If a transgenic plant is released, its interactions with the receiving environment may or may not adversely affect an assessment endpoint. The identification of potential adverse effects may be informed by characteristics of the plant, trait and receiving environment. For example, if pollinator/honeybee survival is selected as an assessment endpoint, a potential adverse effect that could be postulated for assessment is that the trait might affect pollinator/honeybee survival leading to reduced abundance and a reduction in pollination services.

1.2.6. Pathways to harm and corresponding risk hypotheses

Pathways to harm (causal or conditional chains of events) describe the scientifically plausible and necessary steps that would need to occur for release of the particular transgenic plant to result in an adverse effect on the assessment endpoint (Nickson, 2008). When planning the environmental risk/safety assessment, one or more pathways leading to harm may be postulated by the assessor for each potential adverse effect identified for an assessment endpoint.

The simple linear examples of pathways provided in the annexes of this document are for illustrative purposes. In reality, the process is often more complex. For example, there may be more than one plausible pathway to consider when determining whether an assessment endpoint may be adversely affected by the interaction of a transgenic plant with its receiving environment. In addition, multiple, plausible pathways may share some of the same steps.

For each step of a postulated pathway to harm, a corresponding risk hypothesis is formulated that will enable the risk assessor to determine whether the pathway is likely to occur. A risk hypothesis can be evaluated in a number of ways that include but are not limited to using experimental data or information available from the scientific literature, or other relevant information as deemed appropriate by the risk assessor (e.g. climate or herbarium studies). If in the actual environmental risk/safety assessment, the evaluation of a risk hypothesis concludes that a step in a pathway is unlikely to occur, then the likelihood of the harm occurring through that particular pathway most likely is negligible. In practice, some hypotheses may be difficult to evaluate or the evaluation using available information may not produce definitive conclusions regarding the likelihood of a particular step in a pathway. This uncertainty may be addressed through a tier-based testing approach (U.S. EPA, 2007), by consideration of multiple sources of information and lines of evidence (i.e. a weight of evidence approach), or by new studies being undertaken (Devos et al., 2019). Nevertheless, in some cases uncertainties may remain that must be addressed by decision makers and risk managers.

1.2.7. Information elements

Information elements that provide the evidence to evaluate the validity of each risk hypothesis are identified. Such evidence can be obtained from a variety of sources as indicated in the previous paragraph. Information elements may relate to characteristics of the plant, the trait, or the receiving environment, and may be quantitative or qualitative. A single information element may be relevant for the evaluation of multiple risk hypotheses. Information elements are only relevant to the assessment when they address a particular risk hypothesis (Devos et al., 2019).

1.3. Use of environmental considerations in planning an environmental risk/safety assessment

Annexes A-G describe a set of environmental considerations routinely examined by assessors when carrying out risk/safety assessments of transgenic plants intended for environmental release. This set includes:

- **Annex A. Invasiveness and Weediness**: This annex provides illustrative examples when considering whether a transgenic plant has the potential to have adverse effects on the environment due to increased weediness or invasiveness, relative to the comparator.
- **Annex B. Vertical Gene Flow**: This annex provides illustrative examples when considering whether gene flow from a transgenic plant to sexually-compatible plants (weedy relatives, and valued relatives and landraces) might represent an additional, indirect pathway of exposure of the environment to the transgenic plant. Gene flow is not an adverse effect per se, but its consequences may lead to adverse environmental effects, relative to the comparator.
- **Annex C. Organisms (Animals)**: This annex provides illustrative examples when considering whether a transgenic plant has the potential to i) have adverse effects on organisms in the environment and their role in ecological functions including food webs, relative to the comparator, and ii) have adverse effects on human/animal health due to non-dietary exposure, relative to the comparator.
- **Annex D. Soil Functions**: This annex provides illustrative examples when considering whether a transgenic plant has the potential to have adverse effects on soil microbial communities responsible for soil processes and soil functions, relative to the comparator.
- **Annex E. Plant Health**: This annex provides illustrative examples when considering whether a transgenic plant has the potential to have adverse effects on its health and the health of surrounding plants in the environment by having an enhanced ability to act as a host for pests, relative to the comparator.
- **Annex F. Crop Management Practices**: This annex provides illustrative examples when considering whether use of a transgenic plant has the potential to drive changes in crop management practices associated with its cultivation relative to those associated with the cultivation of the comparator, and whether such changes could have adverse effects on the environment.
- **Annex G**. **Biodiversity (Protected Species and Habitats/Ecosystems)**: This annex provides illustrative examples when considering whether a transgenic plant has the potential to have adverse effects on species and habitats explicitly protected by legislation of a country or a region, relative to the comparator, while the six previously- mentioned annexes provide examples when considering a selection of ways in which a transgenic plant has the potential to have adverse effects on species or ecosystems that may have a role in ecological functions and services. Broader aspects of biodiversity may be addressed in an environmental risk assessment for the release of transgenic plant under some jurisdictions.

Each annex is organised in the following manner:

- An introduction describing the environmental consideration.
- Key concepts and terms relevant to the environmental consideration.
- Determination of assessment endpoints.
- Identification of potential adverse effects on the assessment endpoints.
- Identification of plausible pathways to harm, formulation of risk hypotheses, and examples of information elements relevant to the risk hypotheses.

The set of environmental considerations included in the annexes captures many of the types of interactions that can occur between plants (including transgenic plants) and their receiving environments. They are meant to provide a convenient way of planning an environmental risk/safety assessment of a transgenic plant based on the nature of potential biological interactions of a plant with its environment. This set is not taken from any single country's considerations or terminology but is reflective of the aspects widely considered by various countries or regions under their legislative frameworks.

Not all environmental considerations may apply in each risk/safety assessment and those that do apply in a particular case will depend on the characteristics of the plant, trait, and receiving environment, and the interactions amongst them. The relevance of each consideration may also vary based on jurisdictional regulatory schemes and general protection goals. Relevant environmental considerations may be addressed in any order that is appropriate to the environmental risk/safety assessment being planned.

As the document is intended to be illustrative rather than comprehensive, only one or two examples are given for each environmental consideration on how the described approach can be used to plan the environmental risk/safety assessment of a particular transgenic plant. The examples are taken from actual experience gained during risk/safety assessment of transgenic plants that have already been evaluated somewhere in the world including, in particular, herbicide-tolerant and/or insect-resistant maize, cotton, low-erucic acid rapeseed (canola), and soybean. The approach described in this document may be considered for different parental plant types, for traits with less familiarity, or in other situations where a plant may be subject to an environmental risk/safety assessment.

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